1637
20

# ARNOLD & PORTER

**June E. Cohan**
June_Cohan@aporter.com
202.942.5071
202.942.5999 Fax
555 Twelfth Street, NW
Washington, DC 20004-1206

#20



April 14, 2003



Commissioner for Patents
Washington, D.C. 20231

Re: U.S. Patent Application No. 09/394,745
Filed: September 15, 1999
Title: **Nucleic Acid Molecules and Other Molecules Associated with Plants**
Inventors: Dane K. FISHER *et al.*
Atty. Docket: 16517.001/38-21(15454)B

Sir:

The following documents are forwarded herewith for appropriate action by the U.S. Patent and Trademark Office (USPTO):

1. Request for Reconsideration of Applicants' Petition under 37 C.F.R. § 1.144, including Exhibit A (29 pages); and

2. Return postcard.

Please stamp the postcard with the filing date of these documents and return it to our courier.

In the event that extensions of time are necessary to prevent abandonment of this patent application, then such extensions of time are hereby petitioned. Applicants do not believe any fees are due in conjunction with this filing. However, if any fees are required in the present application, then the Commissioner is hereby authorized to charge such fees to Arnold & Porter Deposit Account No. 50-2387, referencing matter number 16517.001/15454B. A duplicate copy of this letter is enclosed.

Respectfully submitted,

June E. Cohan (Reg. No. 43,741)
Holly Logue Prutz (Reg. No. 47,755)

Attachments

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE


In re application of:

Dane K. FISHER *et al.*

Appln. No.: 09/394,745

Filed: September 15, 1999

Title: **Nucleic Acid Molecules and Other Molecules Associated with Plants**

Art Unit: 1637

Examiner: Young J. KIM

Atty. Docket: 16517.001/38-21(15454)B



## Request for Reconsideration of Applicants' Petition under 37 C.F.R. §1.144

Commissioner for Patents
Washington, DC 20231

Sir:

Responsive to the Decision mailed February 14, 2003 in the above-identified application, Applicants hereby petition the Commissioner for reconsideration of their Petition to withdraw the improper restriction requirement. Applicants request the Commissioner to withdraw the restriction to a single grouping of nucleic acid molecules, and to re-open prosecution so that the patentability of the full scope of the pending claims may be considered. This petition is timely filed within two months of mailing of the Decision.

### A. Statement of Facts

1. Application Serial No. 09/394,745, filed September 15, 1999 (the "Application"), discloses 57,264 nucleic acid sequences for expressed sequence tags (ESTs), *i.e.*, short sequences of genes of the plant *Zea mays* (corn) obtained by sequencing from the 5' end of cDNA clones. The sequence listing discloses SEQ ID NOs: 1 – 57264.

2. In the interest of brevity, Applicants will not repeat the full history of the prosecution of the Application, which is fully disclosed in the "Statement of Facts" section (pages 1-5) of Applicants' Petition under 37 C.F.R. § 1.144, filed January 10, 2003 (the "Petition") (attached hereto as Exhibit A).

3. In sum, the Petition set forth reasons and arguments addressed to the improper requirement for restriction to a single grouping of nucleic acid molecules in the Application. The Petition asserted that the restriction requirement (1) is based on a misconstruction of the nature of Applicants' claimed invention and, most importantly, effectively denies Applicants their statutory right to examination of what they regard as their invention; (2) is a misapplication of the directives and standards published in the MPEP; and (3) effectively nullifies the advantages and value of the disclosed invention and is inappropriate in light of the alternative search mechanisms available to the United States Patent and Trademark Office (the "Office"). *See* Petition at page 6.

4. On February 14, 2003, the Director of Technology Center 1600 issued a Decision denying Applicants' Petition (the "Decision"). In brief, the Decision stated that the restriction requirement was proper and summarily dismissed Applicants' contentions and arguments presented in the Petition. *See* Decision at page 2.

5. On March 13, 2003, Applicants filed an Appellant's Brief addressing the outstanding rejections of the claims of the Application under 35 U.S.C. §§ 101 and 112, first paragraph, which is currently under consideration.

**B. Summary of Arguments**

Applicants respectfully petition the Commissioner to reconsider the Decision's denial of their request to withdraw the restriction requirement in the above-captioned matter. Applicants further request that the restriction requirement be withdrawn and prosecution be re-opened in the Application to consider the patentability of the full scope of the pending claims. As presented in the Petition at page 6, the restriction to a single grouping of nucleic acid molecules in the Application is based on a misconstruction of the nature of Applicants' claimed invention and, most importantly, effectively denies Applicants their statutory right to examination of what they regard as their invention.

Furthermore, the restriction requirement misapplies the directives and standards published in the MPEP. Rather than applying appropriate examination procedures for the microarray invention actually claimed by Applicants, the Office insists on applying an examination procedure[1] intended for examining compositions defined by nucleic acid sequences.

Finally, the restriction requirement effectively nullifies the advantages and value of the disclosed invention and is inappropriate in light of the alternative search mechanisms available to the Office. The Office's approach effectively forecloses examination of what Applicants regard as their invention, *i.e.*, the claimed invention. The nature and full scope of the claimed invention cannot be properly examined as restricted, even if Applicants were financially and practically able to file the thousands of divisional applications apparently required by the restriction requirement.

## C. Detailed Arguments

In their Petition, Applicants presented detailed arguments supporting their assertion that the restriction to a single grouping of nucleic acid molecules is improper. While the Decision purports to address Applicants' arguments, it does not appear that the Office gave full consideration to Applicants' stated position. In the interest of brevity, Applicants incorporate herein all of the arguments previously presented in their Petition (attached hereto as Exhibit A), and present below only their response to the arguments made in the Decision.

### (a) The Office misunderstands the nature of the Claimed Invention.

The Decision states that "applicants argue that the examiner, by agreeing to also examine claim 11 *at applicants' request*, 'essentially rewrote claim 8' into a different format." Decision at pages 1-2 (emphasis in original) This assessment misstates Applicants' arguments presented in the Petition.

---

[1] *See* Footnote 4 of the Petition at page 6.

Applicants did not and do not object to the examination of claim 11 together with claims 8-10. What Applicants protest is the Examiner's restriction to a single combination for examination in claims 8-10, which had the effect of changing the scope and nature of claims 8-10, *i.e.*, essentially rewriting claims 8-10 to encompass a different invention than that claimed by Applicants. Applicants did not assert in the Petition that the decision to examine claims 8-11 together essentially rewrote claim 8, but instead presented a comparison of claims 8 and 11 to illustrate how the restriction to a single combination altered the scope of claim 8.

In the Petition, Applicants argued that the Examiner recognized the different scope of the claimed inventions in the Restriction Requirement mailed December 19, 2000, which separated claims 8-10 into group I and claim 11 into group II. Petition at page 2. Applicants also pointed out that the restriction to a single grouping of nucleic acid molecules, which is the subject of this and Applicants' prior Petition, was only applied to group I, claims 8-10. *Id.* at pages 2-3. Thus, Applicants argued that the Examiner recognized that claims 8-10 were of a different scope, and directed to a different invention, than claim 11. To wit, claims 8-10 recites a Markush group, while claim 11, comparatively smaller in scope, recites an actual combination. *Id.* at pages 7-9.

In response to Applicants' request, the Examiner agreed to examine claim 8-11 together, apparently recognizing that conducting a search of the full scope of claims 8-10 would render a further search for claim 11 unnecessary, because claim 11 recites a possible combination of selected elements present in the Markush group of claims 8-10. The Decision also recognized that there was no reason to maintain the restriction requirement between claims 8-10 and claim 11, stating that the Examiner recognized that "having conducted the search for claims 8-10, no further search would be required for claim 11." Decision at page 2.

However, the Examiner did not withdraw the restriction of claims 8-10 to a single grouping of nucleic acids, and it is this restriction that effectively rewrites these claims from presenting alternative groupings of nucleic acids selected from a Markush group, into a

combination claim like claim 11. *See* Petition at page 7. The Decision apparently recognizes that the invention recited in claims 8-10 in fact encompasses "thousands upon thousands of various combinations", but then states that "Applicants may claim as many combinations as they wish. So long as the claimed combinations include SEQ ID NO: 5893". Decision at page 2.

To argue, as the Decision does, that the restriction requirement does not rewrite claims 8-10 is untenable.[2] As described in detail in the Petition, claim 8 as originally presented recites an array having a substrate with a surface comprising a group of nucleic acids, where a subset of the group has a number of recited features which include being complementary to a sequence selected from a Markush group of SEQ ID Nos. Claim 8, therefore, contains multiple variables, including but not limited to: (1) the nature of the group of nucleic acids as a whole; (2) the size of the subset, *e.g.*, 10% of the molecules in the group, 15% of the molecules in the group, etc.; (3) the length of each molecule in the subset, *e.g.*, 250 residues, 250 to 350 residues, etc.; (4) how many, and to which sequences of the Markush group each molecule in the subset is complementary; and (5) to which sequence(s) from the Markush group is the subset as a whole complementary, *e.g.*, all of the molecules in the subset may be complementary to a single sequence from the Markush group, all of the molecules in the subset may be complementary to different sequences from the Markush group, etc. Petition at pages 7-8.

As Applicants previously argued, the restriction of claim 8 and its dependents to a single combination of nucleic acid sequences limits the scope of the claimed invention so greatly as to deny Applicants their statutory right to seek protection for what they regard as their invention. Applicants' invention is not directed to a single nucleotide, a combination of nucleotides, or even

---

[2] What the Decision suggests is that, for example, claim 8 be rewritten, adding the following underlined text, rather than what is *actually* recited in the claim and regarded as Applicants' invention:

> 8. A microarray comprising a substrate with a surface comprising $10^3$ nucleic acid molecules or more where at least 10% of the nucleic acid molecules are comprised of different sequences and at least about 250 nucleotide residues and complementary to a molecule comprising a sequence of SEQ ID NO: 5893 and a sequence selected from the group consisting of [the recited Markush group].

a group of nucleotides, but rather to a manufacture (a microarray) designed to efficiently analyze large numbers of nucleotide sequences for target sequences or a fragment of those sequences; and to the ability to vary and select which sequences to analyze with that manufacture. Forcing Applicants to include SEQ ID NO: 5893 (or any other particular sequence) in every possible combination of sequences on the array destroys the value of the invention, and effectively rewrites the claims to recite an invention different from Applicants' invention.

Therefore, the restriction to a single grouping of nucleic acid molecules redefines the claimed invention and effectively denies Applicants' statutory right to examination of what they regard as their invention.

**(b) The restriction requirement misapplies the directives and standards published in the MPEP.**

The Decision next argues that restriction to a single combination of nucleic acid sequences of claims 8-10 is proper under MPEP § 803.04. Specifically, the Decision states "[t]he claimed microarrays are articles of manufacture comprising compositions similar (if not identical) in nature to the compositions discussed in MPEP 803.04." Decision at page 2. This is not correct.

As Applicants pointed out in the Petition, the Examiner repeatedly attempted to characterize the invention described in claims 8-10 as a combination of nucleic acid sequences, and particularly as a combination of nucleic acids falling under example C of MPEP § 803.04. *See* Petition at page 11. While Applicants do not disagree with the Decision's contention that microarrays are not *per se* new, the novelty of Applicants' invention does not lie in a ***single*** combination of nucleic acid sequences present on the claimed microarrays. Because no single combination, subcombination, collection, or nucleic acid sequence is generic to the claimed microarrays, a restriction that requires all embodiments of the claimed invention to include a single nucleic acid sequence deprives Applicants of their right to have their invention properly

examined. Application of § 803.04 and example C cannot provide for proper examination of Applicants' claimed invention because it is the ability to modify, substitute and select different combinations of nucleic acid molecules with varying features that creates the usefulness of Applicants' claimed microarrays, and therefore this ability is regarded by Applicants as the essence of their invention.

Moreover, as Applicants have previously pointed out, if Applicants are to be granted their statutory right to have what they regard as their invention examined, then examination of the Markush group of claims 8-10, in its entirety, is required. In accordance with the mandate for searching a proper Markush group under MPEP § 803.02, if such a claim can be examined without serious burden, "the examiner must examine all the members of the Markush group in the claim on the merits, even though they are directed to independent and distinct inventions." MPEP § 803.02. Applicants have, in fact, submitted evidence supporting their position that the entire Markush group consisting of the 497 SEQ ID Numbers originally claimed can be examined without serious burden. In contrast, the Examiner has not presented any evidence supporting a contrary position. *See* Petition at page 13.

Therefore, the application of MPEP § 803.04 to Applicants' claimed invention is improper, particularly where the Office has specific guidelines under MPEP § 803.02 for the proper examination of a claim including a Markush group. The restriction requirement violated Applicants' rights and ignored the directives and application of the Office's published guidelines.

**(c) The restriction requirement effectively nullifies the advantages and value of the claimed invention.**

The Decision points out that "[a]t the present time, all prior art searches for U.S. patent applications are performed 'in house.' " Decision at page 2. As Applicants have previously stated, there are several less restrictive, alternative solutions available to aid the Office in its efforts to fairly search and prosecute applications involving nucleotide and amino acid

sequences. These proposed solutions, as well as many others, do not deny an applicant his Constitutional right to the examination of the full scope of his invention. *See* Petition at pages 16-17.

The importance of the biotechnology industry, and its rapid rate of growth, are recognized worldwide. As the biotechnology industry continues to grow, the number of patent applications directed to nucleic acid sequences will also continue to grow. In spite of the widespread availability of modern sequence searching tools already in use by the scientific community, the Office continues to cling to archaic and outdated procedures, even where more efficient, practical, fair and reliable alternatives are immediately available. This attitude hinders the ability of the biotechnology industry to obtain patent protection for their inventions, thereby inhibiting development of the industry.

Furthermore, the assertion in the Decision that all prior art searches for U.S. patent applications are performed "in house", and the implication that a prior art search performed by Applicants is unacceptable to the Office, is simply incorrect. For example, the Office currently provides for an applicant to submit prior art references and certify that he has made or caused to be made a careful and thorough search of the prior art in situations where a Petition to Make Special under 37 C.F.R. § 1.102 has been granted. *See* MPEP § 708.02. Moreover, the Office has acknowledged that "[a]pplicants are generally in the best position to identify the most pertinent prior art related to their invention(s)."[3] Certainly, if the Office has, at the present time, recognized both the importance of biotechnology inventions and the benefit of allowing an applicant to conduct a thorough prior art search and submit the most pertinent references, then

[3] *See also Four-Tracks Patent Examination Process*, Productivity, Pendency 2 at page 9 ("Many times, applicants possess the expertise to recognize and identify the most pertinent prior art patents and publications related to their invention(s). Review of the ISSR will result in applicant identification of significant patentability issues related to novelty and obviousness before an examiner even begins, thus enabling examiners to better spend their time on the analysis of patentability that is critical to patent quality.")

implementing such procedures as those proposed by the 21st Century Strategic Action Plan of June 3, 2002, cannot be merely a futuristic goal of the Office.

Rather, Applicants' offer to assist in searching the prior art for the sequences listed in the claims cannot be summarily dismissed by the Office, as the Decision does. Applicants have not only offered evidence that a prior art search for the entire Markush group consisting of 497 sequences can be performed in a reasonable time frame and without undue burden, but have additionally submitted the results of Applicants' search to the Office for consideration.

In light of the progressive, fair, efficient and less restrictive alternatives presently available to the Office, and the recognized importance of fostering the growth of the biotechnology industry, a blanket policy that only allows an applicant to have a single nucleotide sequence examined in each application filed is inappropriate. Furthermore, it denies Applicants the right to have the full scope of what they regard as their invention examined.

**D. Conclusion**

In view of the arguments above, Applicants specifically petition the Commissioner to review and require withdrawal of the restriction requirement and return this application to the Examiner with instructions to re-open prosecution and examine the full scope of the claimed invention.

The U.S. Patent and Trademark Office is hereby authorized to charge any fee deficiency, and/or credit any overpayment, to our Deposit Account No. 50-2387, referencing docket number 16517.001/15454B. In the event that extensions of time beyond those petitioned for herewith are necessary to prevent abandonment of this patent application, then such extensions of time are hereby petitioned. Applicants do not believe any additional fees are due in conjunction with this filing. However, if any fees under 37 C.F.R. §§ 1.16 or 1.17 are required in the present application, including any fees for extensions of time, then the Commissioner is hereby authorized to charge such fees to Arnold & Porter Deposit Account No. 50-2387, referencing matter number 16517.001/15454B.

Respectfully submitted,

Thomas E Kelley
by JSC Reg # 43,741

Thomas E. Kelley (Reg. No. 29, 938)
by David R. Marsh (Reg. No. 41,408)
June E. Cohan (Reg. No. 43,741)

Date: April 14, 2003

MONSANTO COMPANY
62 Maritime Drive
Mystic, CT 06355
860-572-5274 telephone
860-572-5280 facsimile

ARNOLD & PORTER
The Thurman Arnold Building
555 Twelfth Street, N.W.
Washington, DC 20004-1206
202.942.5000 telephone
202.942.5999 facsimile

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE



In re application of:
Dane K. FISHER *et al.*
Appln. No.: 09/394,745
Filed: September 15, 1999
For: ***Nucleic Acid Molecules and Other Molecules Associated with Plants***

Art Unit: 1637
Examiner: Young J. KIM
Atty. Docket: 16517.001/38-21(15454)B



## Petition under 37 C.F.R. §1.144

Commissioner for Patents
Washington, DC 20231

Sir:

Responsive to the final Office Action mailed September 11, 2002, with a three (3) month shortened statutory period for response, Applicants hereby petition the Commissioner to review and require withdrawal of the requirement for restriction to a single grouping of nucleic acid molecules in the above-identified application and require consideration of the patentability of the full scope of the pending claims. This petition is filed prior to appeal under a petition for extension of time.

### A. Statement of Facts

1. Application Serial No. 09/394,745, filed September 15, 1999 (the "Application"), discloses 57,264 nucleic acid sequences for expressed sequence tags (ESTs,) *i.e.* short sequences of genes of the plant *Zea mays* (corn) obtained by sequencing from the 5' end of cDNA clones. The sequence listing discloses SEQ ID NOs: 1 – 57264. Application at page 9, lines 24 through 26 and page 91, line 5 through page 99, line 26 (Examples 1-2).

2. The Application was originally filed with 7 claims directed to nucleic acid molecules and transformed plants. In a preliminary amendment filed on October 10, 2000 ("Preliminary Amendment"), Applicants canceled all of the original claims and added new claims 8-11. Claim 8 and its dependents were directed, in general, to "a microarray having a substrate with a surface comprising $10^3$ nucleic acid molecules or more where at least 10% of the nucleic acid molecules are different and at least about 250 nucleotide residues and complementary to a nucleic acid

molecule having a sequence selected from a Markush group consisting of [497 nucleotide sequences]".[1]

3. The Remarks section of the Preliminary Amendment explains that Applicants' representative, Linda T. Parker, carried out a computer search on November 3, 1999, of the nonredundant nucleotide database posted by the National Center for Biotechnology Information (NCBI) (ftp://ftp.ncbi.nlm.nih.gov/blast/db/ntz). Preliminary Amendment at page 14. The computer search involved a BLASTN query using the default parameters and SEQ ID NO: 5746 through SEQ ID NO: 8666 as the query sequences. A copy of the BLASTN output was submitted on CD-ROM with the Preliminary Amendment. *Id.* at 15. Based on the output of the BLASTN analysis, the original set of 2961 sequences was reduced to the 497 nucleotide sequences listed in the claims.[2]

4. In the Office Action mailed December 19, 2000 ("Restriction Requirement"), the Examiner restricted the application to one of two groups, with Group I consisting of claims 8-10, drawn to a microarray containing a set of nucleic acid molecules that were not fully characterized, and Group II consisting of claim 11, drawn to a microarray containing a defined set of nucleic acid molecules. Restriction Requirement at page 2. The Examiner also recognized that the "different inventions contain different and distinct sets of nucleic acid molecules and therefore have different structures and functions." *Id.*

5. The Restriction Requirement further stated that in claims 8-10 the subset of nucleic acid sequences "are not clearly defined because the subset is recited as containing 1000 nucleic acid molecules, only 100 of them being unique, selected from a group of approximately 400 nucleic acid molecules. It would be an undue search burden to perform a search on every combination of 100 nucleic acid molecules selected from a set of 400 molecules." Restriction Requirement at page 2. The Restriction Requirement went on to state "[i]t is noted that if applicants claim a

---

[1] The complete text of claims 8-11, as presently pending in the application, are attached hereto as Appendix A. The complete text of claims 8-11, as originally filed in the Preliminary Amendment, are attached hereto as Appendix B.

[2] The selection of the 497 nucleotide sequences included in claims 8-11 was based on identifying, from the original set of 2921 sequences, only those sequences that were greater than 400 nucleotides in length and either had no matches to any public sequence in the queried database or matched for the top hit (best E value; definition available at http://www.ncbi.nlm.nih.gov/Education/BLASTinfo/glossary2.html) to a public sequence in the queried database in only a single high scoring pair of less than 100 nucleotides where the match had an expectation (E value) greater than 1E-3.

combination of nucleotide sequences, the presence of one novel and nonobvious sequence within the combination will render the entire combination allowable." *Id.* The Restriction Requirement further states "a combination of nucleotide molecules comprising a defined group of nucleotide molecules is required." *Id.* at pages 2-3. Thus, the Examiner required that should Applicants select Group I (claims 8-10) for examination, then "Applicants are required to select one combination for examination" and examination "will be restricted to only the elected combination."[3] *Id.* at page 3. As such, only claims 8, 9 and 10 are the subject of the present Petition.

6. In a Response to Restriction Requirement dated April 17, 2001 ("Response to Restriction Requirement"), Applicants provisionally elected, with traverse, the subject matter of Group I, *i.e.* claims 8-10. Response to Restriction Requirement at page 1. In addition, Applicants provisionally elected, with traverse, the first 100 sequences in the Markush group in response to the additional restriction requirement, or election of species, imposed by the Examiner. *Id.* at pages 2-3. Applicants also expressed their belief that it would not pose an undue burden on the Patent Office to examine all of the sequences listed in the claims and, reiterating remarks in the Preliminary Amendment, pointed out that

> It took applicants' representative less than 10 minutes to set up the BLASTN search. After the BLASTN search was completed, Applicants' representative spent approximately 2 hours examining and parsing the BLASTN output with the purpose of selecting those sequences which either had no matches to any sequence in the queried database or which fulfilled other criteria. In this case, the Examiner is being asked to examine only 498 [sic – 497] sequences, rather than approximately 3000. ... To further avoid any undue search burden the PTO is encouraged to refer to the preliminary amendment of October 10, 2000 in which applicant [sic] submitted a copy of the BLASTIN output on CD-ROM.

*Id.* at page 2.

7. In the Office Action mailed May 21, 2001 ("First Office Action"), the Examiner alleged that Applicants' response to the restriction requirement was not fully responsive because although "it appears that Applicants have elected a specific combination of nucleic acids, it is not definite what the elected SEQ ID Numbers are." First Office Action at page 2. The Examiner

---

[3] Applicants assert that this reading of claim 8 and its dependents is improper. The Examiner's requirement that Applicants elect a single combination for examination reflects an improper understanding of the invention disclosed in claim 8. These arguments will be addressed in more detail in Section C, *infra*.

also required Applicants to "specifically recite, on the record, all one hundred SEQ ID numbers that are elected." *Id.*

8. Applicants filed a Reply to Detailed Action on July 3, 2001 ("Reply"), traversing the Patent Office position that the Response to the restriction requirement was not fully responsive. Reply at page 1. It was also reiterated that Applicants had elected with traverse Group I, claims 8-10, "each of which is characterized by the same Markush group of 498 [sic – 497] nucleotide sequences," and that in response to the further restriction requirement, or the election of species as the case may be, Applicants had elected the "first 100 sequences in the Markush group." *Id.* at pages 1-2. To facilitate prosecution, Applicants explicitly recited the 100 sequences from the Markush group selected as the species for examination. *Id.* at pages 2-3.

9. In a second Office Action mailed March 18, 2002 ("Second Office Action"), the Examiner, upon further consideration, withdrew the restriction requirement between Groups I and II and allowed all of the pending claims to be examined together. Second Office Action at page 2. However, in addressing Applicants' repeated objections to the restriction requirement for electing a combination, and Applicants' argument that they had performed a search via BLASTIN for 2921 sequences in a reasonable time frame, the Examiner responded "this argument is not found persuasive because the PTO does not conduct sequence searches in like manner. For each claimed SEQ ID Number, the Office must perform a sequence search, for each SEQ ID Number, on a commercial database (which includes multiple databases), PTO in-house database, and the issued-patent database," and thus there would be an enormous search burden. *Id.* The Examiner further stated that "the examination of SEQ ID Numbers will not go beyond the 100 SEQ ID Numbers." *Id.* (emphasis added). The Examiner made the requirement final without acknowledging Applicants' characterization of the 100 sequences as a Markush group rather than as a combination of 100 sequences. The Second Office Action also recited rejections of the claims under 35 U.S.C. §§ 101 and 112, first paragraph.

10. In an Amendment and Response dated June 18, 2002 ("Amendment"), Applicants amended all of the pending claims to reflect the 100 elected sequences and to correct typographical errors. Amendment at pages 1-3. Applicants further maintained their traversal with respect to the requirement for electing a combination and the restriction requirement limiting the examination to 100 SEQ ID Numbers. *Id.* at page 4. Applicants also pointed out

that "[a]rrays of nucleic acid sequence[s] are commonly employed where a single array on a solid support contains thousands of separated nucleic acid sequences. To require an applicant to file hundreds of applications to cover a single product would serve only to effectively deprive applicant of patent rights on his invention." *Id.* Applicants also argued against the outstanding rejections of the claims under Sections 101 and 112.

11. In a final Office Action mailed on September 11, 2002 ("Final Office Action"), the Examiner maintained the rejections of the claims under Sections 101 and 112. Pertinent to the present Petition, the Examiner acknowledged Applicants' traversal "with regard to the restriction of the claims into a specific combination of 100 SEQ ID Numbers". Final Office Action at page 2. The Examiner further stated that

> Applicants are advised that the actual combination of 'one hundred' SEQ ID Numbers was selected by Applicants, and was not required by the Examiner. Applicants were requested to elect a single combination of nucleic acids to which Applicants have elected the 'first one hundred' SEQ ID Numbers as the elected combination. In other words, Applicants could have elected all of the recited SEQ ID Numbers as the combination to be examined. However, it was Applicants who have decided to elect the first 100 SEQ ID Numbers as the elected combination.

*Id.* The Examiner also acknowledged that

> It appears Applicants are traversing the restriction requirement wherein Applicants were required to elect a single combination. If Applicants are traversing that such requirement should not have been made, Applicants are referred to MPEP 803.04, example C, wherein it explicitly states that such combination claims would be subject to restriction requirement wherein Applicants will be required to 'select one combination for examination'. However, if Applicants are traversing at [sic] the fact that only 100 SEQ ID Numbers were examined as the elected combination, Applicants are advised that it was Applicants who have decided to elect the first 'one hundred SEQ ID Numbers' as the combination to be examined.

Final Office Action at page 2.

**B. Summary of Arguments**

Applicants respectfully petition the Commissioner to review and require withdrawal of the requirement for restriction to a single grouping of nucleic acid molecules and require consideration of the patentability of the full scope of the pending claims.

This restriction requirement is based on a misconstruction of the nature of Applicants' claimed invention and, most importantly, effectively denies Applicants their statutory right to examination of what they regard as their invention.

Furthermore, this restriction requirement is a misapplication of the directives and standards published in the MPEP. Rather than applying appropriate examination procedures for the microarray invention actually claimed by Applicants, the Examiner insists on applying an examination procedure[4] intended for examining compositions defined by nucleic acid sequences.

Finally, this restriction requirement effectively nullifies the advantages and value of the disclosed invention and is inappropriate in light of the alternative search mechanisms available to the United States Patent and Trademark Office ("USPTO"). The USPTO's insistence on archaic procedures and policies where more efficient, fair and reliable alternatives are available forces Applicants to face an economic burden of filing thousands of applications for any invention containing subject matter directed to nucleotide or amino acid sequences. Moreover, even this expenditure would not allow Applicants to effectively claim what they regard as their invention.

---

[4] The U.S. PTO implemented a policy specific to the examination of inventions directed to nucleotide sequences, published in 1192 O.G. 68 (November 19, 1996). As published, the U.S. PTO has a policy of searching up to ten sequences. The basis for that policy is that each sequence defines an independent and distinct invention. The U.S. PTO further codified this policy in MPEP §803.04:

> Nucleotide sequences encoding different proteins are structurally distinct chemical compounds and are unrelated to one another. These sequences are thus deemed to normally constitute independent and distinct inventions within the meaning of 35 U.S.C. 121. Absent evidence to the contrary, each such nucleotide sequence is presumed to represent an independent and distinct invention, subject to a restriction requirement pursuant to 35 U.S.C. 121 and 37 CFR 1.141 *et seq.* Nevertheless, to further aid the biotechnology industry in protecting its intellectual property without creating an undue burden on the Office, the Commissioner has decided *sua sponte* to partially waive the requirements of 37 CFR 1.141 *et seq.* and permit a reasonable number of such nucleotide sequences to be claimed in a single application. See *Examination of Patent Applications Containing Nucleotide Sequences,* 1192 O.G. 68 (November 19, 1996).
>
> It has been determined that normally ten sequences constitute a reasonable number for examination purposes. Accordingly, in most cases, up to ten independent and distinct nucleotide sequences will be examined in a single application without restriction. In addition to the specifically selected sequences, those sequences which are patentably indistinct from the selected sequences will also be examined. Furthermore, nucleotide sequences encoding the same protein are not considered to be independent and distinct inventions and will continue to be examined together.

The unofficial policy now implemented by the U.S. PTO, with respect to applications claiming nucleotide or amino acid sequences, is an outright refusal to examine more than a single sequence in any application. The U.S. PTO altered this policy without soliciting any comment from the public or publishing its new policy.

**C. The Detailed Arguments**

**(a) This restriction requirement is based on a misconstruction of the nature of Applicants' claimed invention and, most importantly, effectively denies Applicants their statutory right to their invention.**

The restriction requirement to elect a single combination for examination denies Applicants their statutory right to seek protection for they regard as their invention. The Restriction Requirement separated out claims 8-10 into Group I and claim 11 into Group II. Although restriction between these groups was later withdrawn, the initial identification of the difference between the scope of claims 8-10 versus claim 11 is important to identify.

The present Petition contests application of the restriction requirement to elect a combination for examination to claims 8-10; no such restriction was ever applied to claim 11. The Restriction Requirement states "[i]f group 1 (claims 8-10) is selected, examination will be restricted to the elected combination." Restriction Requirement at page 3. As will be explained in greater detail *infra*, such a restriction was an attempt by the Examiner to rewrite claims 8-10 as a claim sharing the format of claim 11. This impermissible action by the Examiner deprived Applicants of their invention.

Claim 8, as originally filed in the Preliminary Amendment, was directed to a microarray having a substrate with a surface comprising $10^3$ nucleic acid molecules or more where at least 10% of the nucleic acid molecules (1) are different and (2) at least about 250 nucleotide residues and (3) complementary to a molecule having a sequence selected from a Markush group. *See* claim 8 in Appendix B. Dependent claims 9 and 10 further recited microarrays where at least 75% and 95%, respectively, of the nucleic acid molecules are different. As such, there are a variety of collections or combinations claimed. For example, claim 8 includes a subset of nucleic acid molecules where 10% of those molecules have the recited features. Claim 8 also includes a subset of nucleic acid molecules where 15% of those molecules have the recited features. Furthermore, claim 8 includes a subset of nucleic acid molecules where 25% of those molecules have the recited features. Each and every single permutation of these nucleic acid molecules is one collection or combination included in the claimed invention.

However, the collections or combinations do not stop there. Within claim 8 and its dependents, there is a subcombination of elements. The second portion of claim 8 is directed to

a Markush group under MPEP §2173.05(h). This Markush group of 497 nucleic acid sequences, as originally claimed, may be combined in countless ways with every possible permutation of the nucleic acid molecules required by the first part of claim 8. For example, a permissible embodiment of a microarray according to claim 8 may include a substrate with a surface where 10% of the nucleic acid molecules of that substrate are comprised of different sequences, the sequences range from 250 to 350 nucleotide residues in length, and each and every one of those molecules comprises a nucleic acid sequence that is complementary to one of the specified sequences in the Markush group, *e.g.*, SEQ ID NO: 5776.[5] Another permissible embodiment of claim 8 may include a substrate where 10% of the nucleic acid molecules of that substrate are comprised of different sequences, every sequence is 250 nucleotide residues in length, but every molecule comprises a nucleic acid sequence that is complementary to a different SEQ ID NO selected from the Markush group of 497 sequences.[6] When examined in this light, it becomes abundantly clear that there are thousands upon thousands of permutations within both the combination and subcombination of Applicants claimed invention, and any permutation of the combination may be combined with any permutation of the subcombination.

In contrast, claim 11 is directed to a single collection or combination of elements. In claim 11, the only variable in the claimed invention is the length of the nucleic acid sequences themselves. The microarray of claim 11 requires that every nucleic acid molecule comprise a nucleic acid sequence that is complementary to each and every SEQ ID NO listed in the claim. Claim 11 does not include the alternative language of the Markush group found in claim 8. By requiring Applicants to select a single combination for examination in the Restriction Requirement, the Examiner essentially rewrote claim 8 into a claim sharing a format similar to

---

[5] For example, in this embodiment of the claimed microarray, the 100 different sequences could be of the form:

[common sequence]
[common sequence]a
[common sequence]at
[common sequence]atg
[common sequence]atgg
[common sequence]atgga
[common sequence]atggac...

where the common sequence is, for example, 250 nucleotides of any SEQ ID NO listed in the recited Markush group, such as SEQ ID NO: 5776.

[6] For example, in this embodiment of the claimed microarray, the 100 different sequences are complementary to SEQ ID NO 5776 and 5781 and 5782 and 5783, etc., *i.e.*, no two nucleic acid molecules comprise sequences that are complementary to the same SEQ ID NO of the Markush group.

that of claim 11 even though the Examiner clearly recognized that these two claims had "different structures and functions." Restriction Requirement at page 2 and Facts *supra* at Paragraph 4 (emphasis added). Not only did this action deprive Applicants of the right to claim what they regard as their invention, but it also ignored the language, limitations, and varying scope for each of the respective inventions claimed.

In a simple analogy, Applicants' invention is like a candy store which dispenses bags of multi-flavor jelly beans. Each bag has at least 100 jelly beans in it and each jelly bean in every bag may be any one of 497 flavors. By restricting Applicants to a single combination for examination, the Examiner forced Applicants to choose one bag of jelly beans as the invention. However, as can be seen in this analogy, no single bag is generic to the entire candy store, nor would examination of any single bag even come close to examining Applicants' invention. In this analogy, Applicants' invention provides a unique product which can be designed or selected in a variety of combinations. Applicants request the same breadth of scope for their invention which is accorded to inventors of claims examined in all other art units.

Applicants have disclosed and claimed a broad invention – a microarray that comprises several thousands of possible variations of nucleic acid molecules comprising different nucleic acid sequences. No single variation is generic to the claimed invention, rather it is the ability to modify, substitute and select different collections or combinations of nucleic acid molecules that creates the usefulness of Applicants' microarray. Applicants' invention is not a fixed microarray, but rather the invention provides the ability to vary the contents of a microarray within the parameters set forth in the claim. Any attempt by the Examiner to restrict this ability by imposing an inappropriate and improper restriction requirement to elect a single combination abrogates Applicants' right to claim what they regard as their invention. The Examiner clearly understood the broad scope of Applicants' invention and its usefulness, as evidenced by the characterization of Group I set forth in the Restriction Requirement as a microarray containing a set of nucleic acid molecules that was not fully characterized. *See* Facts *supra* at Paragraph 4. Regardless, the Examiner attempted to severely limit the scope of Applicants' invention to the point of redefining it altogether.

Ironically, Applicants' response to the restriction requirement to elect a single combination for examination and the Examiner's application of MPEP § 803.04 to claim 8 only

serves to further highlight the inappropriateness of the restriction requirement in the first place. In response to the restriction requirement, Applicants were forced to elect a species for examination in order to fully reply to the outstanding office action. *See* Response to Restriction Requirement at pages 2-3 and Facts *supra* at Paragraph 6. Applicants elected, with traverse "the first 100 sequences in the Markush group." *Id.* Although claim 8 was later amended to explicitly recite only these 100 sequences, the overall structure of the claim remained unchanged. Thus, even though the first 100 sequences in the Markush group were elected, Applicants claimed invention would still include thousands upon thousands of various combinations and permutations within both the combination and subcombination, as explained above.

For the Examiner's part, the refusal to examine the claim as anything other than falling under the ambience of MPEP § 803.04, example C, enunciates the mischaracterization of the claimed invention. It disregards the nature of the alternative language of the Markush group and forces the claimed invention to be examined under a procedure that is completely inappropriate.

The restriction of claim 8 and its dependents to a single combination of nucleic acid sequences limits the scope of the claimed invention so greatly as to deny the invention entirely. Applicants are not claiming nucleic acid molecules or nucleotide sequences in isolation. The claims are directed to a microarray that allows one to efficiently analyze large amounts of nucleotide sequences for a target sequence or a fragment of that sequence. Implementing a requirement that Applicants elect a combination of nucleic acid sequences in the present application effectively destroys the value of the invention as a manufacture for efficiently analyzing large amounts of nucleotide sequences and is an attempt to rewrite the claims to another invention. As stated above, Applicants' invention is not directed to a single nucleotide, a combination of nucleotides, or even a group of nucleotides, but rather to a manufacture designed to efficiently analyze large amounts of nucleotide sequences for target sequences or a fragment of those sequences; and the ability to vary and select which sequences to analyze in that manufacture.

**(b) This restriction requirement is a misapplication of the directives and standards published in the MPEP.**

Applicants were denied the ability to seek their statutory rights in the disclosed invention almost immediately during prosecution of the present application due to the Examiner's

improper application of the directives set forth in the MPEP. In particular, the Examiner misapplied MPEP § 803.04 to claims 8-10 without considering what Applicants had laid out in the claims as their invention.

In the Restriction Requirement, the Examiner mischaracterized the invention as a combination of nucleic acid sequences falling under § 803.04, stating that

> a combination of nucleotide molecules comprising a defined group of nucleotide molecules is required. Applications containing claims reciting different combinations of individual nucleotide sequences (as in 'a combination of DNA fragments, said combination containing at least thirty different DNA fragments selected from SEQ ID NOS. 1-1000') are subject to a restriction requirement.

Restriction Requirement at pages 2-3 (emphasis added). This mischaracterization is reiterated by the Examiner in the Final Action when it states

> [i]f Applicants are traversing that such a requirement should not have been made, Applicants are referred the MPEP 803.04, example C, wherein it explicitly states that such combination claims would be subject to restriction requirement wherein Applicants would be required to 'select one combination for examination.'

Final Action at page 2. What the Examiner failed to recognize is that Applicants' claims are not solely directed to different combinations of individual nucleotide sequences, or even to compositions comprising nucleotide sequences. The claims are directed to an article of manufacture, *i.e.*, a microarray.

As discussed in footnote 4 *supra*, the USPTO has adopted a special policy with respect to the examination of nucleic acid sequences, codified at MPEP §803.04, wherein the USPTO has announced publicly its intention to waive the requirements of 37 C.F.R. § 1.141 and examine up to ten nucleic acid sequences. The published examples of typical nucleotide sequence claims impacted by the partial waiver of 37 C.F.R. § 1.141 are as follows:

> Examples of typical nucleotide sequence claims impacted by the partial waiver of 37 CFR 1.141 *et seq.* (and the partial waiver of 37 CFR 1.475 and 1.499 *et seq.*, see MPEP § 1850) include:
>
> (A) an isolated and purified DNA fragment comprising DNA having at least 95% identity to a DNA sequence selected from SEQ ID Nos. 1-1,000;
> (B) a combination of DNA fragments comprising SEQ ID Nos. 1-1,000; and
> (C) a combination of DNA fragments, said combination containing at least thirty different DNA fragments selected from SEQ ID Nos. 1-1,000.
>
> *****

> Applications containing only composition claims reciting different combinations of individual nucleotide sequences, such as set forth in example (C), will be subject to a restriction requirement. Applicants will be required to select one combination for examination. If the selected combination contains ten or fewer sequences, all of the sequences of the combination will be searched. If the selected combination contains more than ten sequences, the combination will be examined following the procedures set forth above for example (B). More specifically, the combination will be searched until one nucleotide sequence is found to be allowable with the examiner choosing the order of search to maximize the identification of an allowable sequence. The identification of any allowable sequence(s) will cause all combinations containing the allowed sequence(s) to be allowed.

MPEP §803.04 (emphasis added). However, simply because the USPTO has devoted a particular section of the MPEP to the examination of some claims that include nucleic acid sequences, it does not entitle an Examiner to automatically apply this section and only this section to every claim which may contain a recitation of a nucleic acid sequence. The examiner must first ascertain an applicant's claimed invention. Only then can examination of the claimed invention be properly addressed under the guidelines published in the MPEP.

The Examiner must examine the claimed invention following the mandates of published USPTO policy. The MPEP is a directive and requires compliance by USPTO employees. *See In re Int'l Flavors & Fragrances, Inc.* 183 F.3d 1361, 1366, 51 U.S.P.Q.2d 1513 (Fed. Cir. 1999) ("although [the MPEP] does not have the force of law, is well known to those registered to practice in the PTO and reflects the presumptions under which the PTO operates") *citing Critikon, Inc. v. Becton Dickinson Vascular Access, Inc.*, 120 F.3d 1253, 1257, 43 U.S.P.Q.2d 1666, 1669 (Fed. Cir. 1997); *In re Portola Pkg., Inc.* 110 F.3d 786, 788, 42 U.S.P.Q.2d 1295, 1297 (Fed. Cir. 1997) ("[t]he MPEP does not have the force and effect of law; however, it is entitled to judicial notice as the agency's official interpretation of statutes and regulations, provided it is not in conflict with the statutes and regulations") *citing Refac Int'l, Ltd. v. Lotus Dev. Corp.*, 81 F.3d 1576, 1584 n.2, 38 U.S.P.Q.2d 1665, 1671 n.2 (Fed. Cir. 1996).

As explained in Section C(a) *supra*, Applicants' invention is directed to an article of manufacture, *i.e.*, a microarray that comprises several thousands of various combinations of elements, with the ability to vary those combinations of elements within the parameters set forth in the claims such that the content of the microarray is not fixed. The Examiner relies on Example C found in § 803.04, however, this example is presented for claims directed to compositions of matter. It does not and cannot be adequately applied to articles of manufacture.

In fact, application of § 803.04 and example C cannot provide for proper examination of Applicants' claimed invention because it is the ability to modify, substitute and select different combinations of nucleic acid molecules with varying features that creates the usefulness of Applicants' microarray; and hence is regarded by Applicants as the essence of their invention. Restricting examination of the claimed invention to that provided for in § 803.04 eliminates that ability altogether because no single subcombination of nucleic acid molecules is generic to the claimed microarray.

If Applicants are to be granted their statutory right to have what they regard as their invention examined, then examination of the Markush group, in its entirety, is required. In accordance with the mandate for searching a proper Markush group under MPEP §803.02, if such a claim can be examined without serious burden, "the examiner must examine all the members of the Markush group in the claim on the merits, even though they are directed to independent and distinct inventions." MPEP § 803.02.[7] Applicants have facilitated this process for the Examiner by submitting the results of their search on CD-ROM for the Examiner's consideration and convenience. *See* Facts *supra* at Paragraphs 3 and 6. Moreover, it is improper for the USPTO to refuse to examine that which Applicants regard as their invention, unless the subject matter in a claim lacks unity of invention.[8] *In re Harnish*, 631 F.2d 716, 206 U.S.P.Q. 300 (C.C.P.A. 1980); *Ex parte Hozumi*, 3 U.S.P.Q.2d 1059 (Bd. Pat. App. & Int. 1984); MPEP § 803.02. The Examiner has refused to follow this mandate without presenting any evidence to support his position.

According to the guidelines for examination of a Markush group under MPEP § 803.02, Applicants will be required to elect a single species for examination. If no prior art is found that anticipates or renders obvious the elected species, then the search of the Markush-type claim will be extended to non-elected species to the extent necessary to determine the patentability of the

---

[7] Applicants have submitted evidence supporting their position that the entire Markush group consisting of the 497 SEQ ID Numbers originally claimed can be examined without serious burden. *See* Facts *supra* at Paragraph 6. In contrast, the Examiner has presented no evidence supporting a contrary position.

[8] In the present case, unity of the nucleic acid sequences within the claimed Markush group exists, for example, by virtue of their common utility in a microarray of nucleic acid molecules as gene-specific hybridization targets to quantitatively measure expression of corresponding plant genes in *Zea mays*. Application at page 59, line 25 through page 60, line 6.

Markush-type claim. MPEP § 803.02. Under this process, the entire 497 nucleic acid sequences originally included in the Markush group of claim 8 would be examined.

Indeed, examination of the entire Markush group of claim 8 is the only way that Applicants may be granted their statutory rights to examination of what they regard as their invention. For example, if the Examiner were to follow the USPTO's policy with respect to the examination of nucleic acid sequences found in MPEP § 803.04, rather than the mandate set forth in § 803.02, no more than ten sequences would be examined. This would not allow Applicants to claim what they regard as their invention. The disclosed and claimed invention is a microarray that allows one to efficiently analyze large amounts of nucleotide sequences for a target sequence or a fragment of that sequence, and to vary the parameters of that search based on the available nucleic acid sequences. Limiting the scope of examination to only a few nucleic acid sequences effectively nullifies the value of the invention as a manufacture for efficiently analyzing large amounts of nucleic acid molecules comprising varied nucleotide sequences, eliminates the flexibility of the manufacture, and is an attempt to rewrite the claims to another invention. Such action violates Applicants' rights and ignores the directives and application of the USPTO's published guidelines.

**(c) This restriction requirement effectively nullifies the advantages and value of the disclosed invention and is inappropriate in light of the alternative search mechanisms available to the USPTO.**

The biotechnology industry is a rapidly changing and progressive arena with ever increasing demands to facilitate its development. Advancements in this industry have consequential implications in numerous other areas, such as medicine, agriculture, security and the military. Yet despite the accelerated pace of research and development in this industry, the USPTO clings to its outdated procedures and policies for examination of nucleic acid and amino acid sequences, even where more efficient, fair and reliable alternatives are available.

Comments solicited by the USPTO prior to the implementation of the policy published in 1192 O.G. 68 (November 19, 1996) show that the biotechnology industry offered several alternatives to the USPTO for examination of applications involving nucleotide or amino acid sequences. These comments demonstrate that although several industry leaders were ready, willing, and able to offer assistance to the USPTO in its efforts to fairly examine the massive

influx of biotechnology applications, the USPTO rejected all of these suggestions in favor of restricting the number of sequences that would be examined in a given application.

For example, several speakers over two days of testimony suggested the USPTO use some standard to eliminate the redundancy of sequences present in the current data bases used by the USPTO in its search efforts. *See, e.g., Hearing and Request for Comments on Issues Relating to Patent Protection for Nucleic Acid Sequences* (hereinafter, "Hearings"), April 16, 1996 at page 11, lines 11 through 19; page 41, line 20 through page 42, line 13. Furthermore, it was also suggested many times that the USPTO use somewhat less sensitive searches because distantly related sequences were being detected much of the time that could have no possible impact on either anticipation or obviousness for the sequence being searched. *See, e.g., Hearings*, April 16, 1996, at page 11, line 20 through page 12, line 5; page 14, lines 8 through 25; *Hearings,* April 23, 1996 at page 7 (line numbers omitted from transcript).

Additionally, the testimony of various people and companies in the field of biotechnology and bioinformatics refutes the USPTO's position that there is simply no feasible way to search these sequences. Several private companies have successfully searched hundreds and even thousands of sequences daily. *See, e.g., Hearings,* April 16, 1996 at page 54, lines 3 through 14, page 72, line 2 through page 73, line 12, *Hearings,* April 23 at page 13. Many companies even perform several searches on their own before submitting an application in order to ensure the subject matter is worth developing. *Hearings,* April 16, 1996 at page 53, line 21 through page 55, line 28.

The USPTO recognizes the difficulties in examination of biotechnology applications and has recently proposed changes to current USPTO policy and examination procedures. *See* The 21st Century Strategic Action Plan, June 3, 2002 ("Plan"). The Plan identifies the challenges of searching and examining more than one nucleic or amino acid sequence and the burden posed by the search and examination of multiple sequences. *See Restriction Practice for Markush and Sequence Claims*, Capability, Legislation/Rules 1 at page 1 ("Restriction Practice"). However, the Plan suggests how this burden may be eliminated without depriving an applicant rights in his claimed invention. The USPTO acknowledges that "[a]pplicants are generally in the best

position to identify the most pertinent prior art related to their invention(s)."[9] Restriction Practice at page 1. One proposal under the Plan would allow an applicant to perform a prior art search, use a commercial searching authority, or use a searching authority certified by the USPTO. The applicant would then be required to submit an information disclosure statement, including a statement of relevancy, with the results of that search. *See Mandatory Information Disclosure Statements (IDS)*, Capability, Legislation/Rules 1a. It is also suggested that this procedure be utilized in one of a four-track patent examination process to decrease the search burden on the USPTO. *See Four-Tracks Patent Examination Process*, Productivity, Pendency 2.

Applicants' own experience supports the position that these proposals are particularly well-tailored to applications involving the examination of nucleotide or amino acid sequences. For instance, based on Applicants' experience with multi-sequence queries to public sequence databases, *e.g.* NCBI (http://www.ncbi.nlm.nih.gov/); the European Molecular Biology Laboratory (EMBL) (http://www.embl-heidelberg.de/); Swiss-Prot (http://www.expasy.org/sprot/sprot-top.html); Derwent life sciences (http://www.derwent.com/geneseq/); etc., relevant prior art can be easily ascertained and assembled for submission to the USPTO. Furthermore, the added cost of multi-sequence searching in these databases is merely a small increment of the cost of a single sequence search. To substantiate this position, Applicants have performed their own search of the nucleic acid sequences encompassed in the Markush group of the present invention and have facilitated the process for the USPTO by submitting their search results on CD-ROM. *See* Facts *supra* at Paragraphs 3 and 6 and footnote 2. In light of this information, Applicants would gladly perform prior art searches in conjunction with the preparation of an application, or utilize a private search service commissioned by the USPTO and pay a real cost search fee. Along these same lines, another possible alternative would be for the Commissioner to petition Congress to amend the law to require publication of all applications with the associated sequence listings so that Applicants themselves could perform novelty searches after 18 months from filing. As Applicants have argued, there are several less restrictive, alternative solutions available to aid the USPTO in its efforts to fairly search and prosecute applications

---

[9] *See also Four-Tracks Patent Examination Process*, Productivity, Pendency 2 at page 9 ("Many times, applicants possess the expertise to recognize and identify the most pertinent prior art patents and publications related to their invention(s). Review of the ISSR will result in applicant identification of significant patentability issues related to novelty and obviousness before an examiner even begins, thus enabling examiners to better spend their time on the analysis of patentability that is critical to patent quality.")

involving nucleotide and amino acid sequences. These proposed solutions, as well as many others, do not deny an applicant his Constitutional right to the full scope of the invention to which he is entitled.

**D. Conclusion**

In view of the arguments above, Applicants specifically petition the Commissioner to review and require withdrawal of the restriction requirement and return this application to the Examiner with instructions to re-open prosecution and examine the full scope of the claimed invention.

The U.S. Patent and Trademark Office is hereby authorized to charge any fee deficiency, and/or credit any overpayment, to our Deposit Account No. 50-2387, referencing docket number 16517.001/15454B. In the event that extensions of time beyond those petitioned for herewith are necessary to prevent abandonment of this patent application, then such extensions of time are hereby petitioned. Applicants do not believe any additional fees are due in conjunction with this filing. However, if any fees under 37 C.F.R. §§ 1.16 or 1.17 are required in the present application, including any fees for extensions of time, then the Commissioner is hereby authorized to charge such fees to Arnold & Porter Deposit Account No. 50-2387, referencing matter number 16517.001/15454B. A duplicate copy of this letter is enclosed.

Respectfully submitted,

Thomas E. Kelley

Thomas E. Kelley (Reg. No. 29, 938)
by David R. Marsh (Reg. No. 41,408)
June E. Cohan (Reg. No. 43,741)

Date: January 10, 2003

MONSANTO COMPANY
62 Maritime Drive
Mystic, CT 06355
860-572-5274 telephone
860-572-5280 facsimile

ARNOLD & PORTER
The Thurman Arnold Building
555 Twelfth Street, N.W.
Washington, D.C. 20004-1206
202.942.5000 telephone
202.942.5999 facsimile

# Appendix A

**Claims as Amended in the Response filed June 18, 2002**

8. A microarray comprising a substrate with a surface comprising $10^3$ nucleic acid molecules or more where at least 10% of the nucleic acid molecules are comprised of different sequences and at least about 250 nucleotide residues and complementary to a molecule comprising a sequence selected from the group consisting of SEQ ID NO: 5776, SEQ ID NO: 5781, SEQ ID NO: 5782, SEQ ID NO: 5783, SEQ ID NO: 5785, SEQ ID NO: 5787, SEQ ID NO: 5800, SEQ ID NO: 5804, SEQ ID NO: 5815, SEQ ID NO: 5818, SEQ ID NO: 5821, SEQ ID NO: 5823, SEQ ID NO: 5828, SEQ ID NO: 5830, SEQ ID NO: 5832, SEQ ID NO: 5836, SEQ ID NO: 5838, SEQ ID NO: 5840, SEQ ID NO: 5845, SEQ ID NO: 5849, SEQ ID NO: 5850, SEQ ID NO: 5851, SEQ ID NO: 5856, SEQ ID NO: 5859, SEQ ID NO: 5863, SEQ ID NO: 5868, SEQ ID NO: 5871, SEQ ID NO: 5874, SEQ ID NO: 5875, SEQ ID NO: 5877, SEQ ID NO: 5893, SEQ ID NO: 5896, SEQ ID NO: 5901, SEQ ID NO: 5908, SEQ ID NO: 5909, SEQ ID NO: 5920, SEQ ID NO: 5922, SEQ ID NO: 5926, SEQ ID NO: 5928, SEQ ID NO: 5929, SEQ ID NO: 5931, SEQ ID NO: 5936, SEQ ID NO: 5937, SEQ ID NO: 5939, SEQ ID NO: 5941, SEQ ID NO: 5944, SEQ ID NO: 5945, SEQ ID NO: 5950, SEQ ID NO: 5955, SEQ ID NO: 5960, SEQ ID NO: 5961, SEQ ID NO: 5963, SEQ ID NO: 5964, SEQ ID NO: 5968, SEQ ID NO: 5973, SEQ ID NO: 5974, SEQ ID NO: 5991, SEQ ID NO: 5994, SEQ ID NO: 5999, SEQ ID NO: 6000, SEQ ID NO: 6001, SEQ ID NO: 6005, SEQ ID NO: 6006, SEQ ID NO: 6007, SEQ ID NO: 6011, SEQ ID NO: 6017, SEQ ID NO: 6018, SEQ ID NO: 6022, SEQ ID NO: 6023, SEQ ID NO: 6026, SEQ ID NO: 6030, SEQ ID NO: 6033, SEQ ID NO: 6042, SEQ ID NO: 6046, SEQ ID NO: 6059, SEQ ID NO: 6063, SEQ ID NO: 6065, SEQ ID NO: 6066, SEQ ID NO: 6089, SEQ ID NO: 6091, SEQ ID NO: 6098, SEQ ID NO: 6106, SEQ ID NO: 6107, SEQ ID NO: 6110, SEQ ID NO: 6117, SEQ ID NO: 6121, SEQ ID NO: 6124, SEQ ID NO: 6131, SEQ ID NO: 6137, SEQ ID NO: 6141, SEQ ID NO: 6144, SEQ ID NO: 6145, SEQ ID NO: 6147, SEQ ID NO: 6154, SEQ ID NO: 6167, SEQ ID NO: 6168, SEQ ID NO: 6170, SEQ ID NO: 6173, SEQ ID NO: 6178, and SEQ ID NO: 6181.

9. A microarray according to claim 8 where at least 75% of the nucleic acid molecules are comprised of different sequences and at least about 250 nucleotide residues and complementary to a molecule comprising a sequence selected from said group.

10. A microarray according to claim 8 where at least 95% of the nucleic acid molecules are comprised of different sequences and at least about 250 nucleotide residues and complementary to a molecule comprising a sequence selected from said group.

11. A microarray comprising nucleic acid molecules that are comprised of different sequences and at least about 250 nucleotide residues, wherein said nucleic acid molecules comprise nucleic acid sequences complementary to SEQ ID NO: 5776, SEQ ID NO: 5781, SEQ ID NO: 5782, SEQ ID NO: 5783, SEQ ID NO: 5785, SEQ ID NO: 5787, SEQ ID NO: 5800, SEQ ID NO: 5804, SEQ ID NO: 5815, SEQ ID NO: 5818, SEQ ID NO: 5821, SEQ ID NO: 5823, SEQ ID NO: 5828, SEQ ID NO: 5830, SEQ ID NO: 5832, SEQ ID NO: 5836, SEQ ID NO: 5838, SEQ ID NO: 5840, SEQ ID NO: 5845, SEQ ID NO: 5849, SEQ ID NO: 5850, SEQ ID NO: 5851, SEQ ID NO: 5856, SEQ ID NO: 5859, SEQ ID NO: 5863, SEQ ID NO: 5868, SEQ ID NO: 5871, SEQ ID NO: 5874, SEQ ID NO: 5875, SEQ ID NO: 5877, SEQ ID NO: 5893, SEQ ID NO: 5896, SEQ ID NO: 5901, SEQ ID NO: 5908, SEQ ID NO: 5909, SEQ ID NO: 5920, SEQ ID NO: 5922, SEQ ID NO: 5926, SEQ ID NO: 5928, SEQ ID NO: 5929, SEQ ID NO: 5931, SEQ ID NO: 5936, SEQ ID NO: 5937, SEQ ID NO: 5939, SEQ ID NO: 5941, SEQ ID NO: 5944, SEQ ID NO: 5945, SEQ ID NO: 5950, SEQ ID NO: 5955, SEQ ID NO: 5960, SEQ ID NO: 5961, SEQ ID NO: 5963, SEQ ID NO: 5964, SEQ ID NO: 5968, SEQ ID NO: 5973, SEQ ID NO: 5974, SEQ ID NO: 5991, SEQ ID NO: 5994, SEQ ID NO: 5999, SEQ ID NO: 6000, SEQ ID NO: 6001, SEQ ID NO: 6005, SEQ ID NO: 6006, SEQ ID NO: 6007, SEQ ID NO: 6011, SEQ ID NO: 6017, SEQ ID NO: 6018, SEQ ID NO: 6022, SEQ ID NO: 6023, SEQ ID NO: 6026, SEQ ID NO: 6030, SEQ ID NO: 6033, SEQ ID NO: 6042, SEQ ID NO: 6046, SEQ ID NO: 6059, SEQ ID NO: 6063, SEQ ID NO: 6065, SEQ ID NO: 6066, SEQ ID NO: 6089, SEQ ID NO: 6091, SEQ ID NO: 6098, SEQ ID NO: 6106, SEQ ID NO: 6107, SEQ ID NO: 6110, SEQ ID NO: 6117, SEQ ID NO: 6121, SEQ ID NO: 6124, SEQ ID NO: 6131, SEQ ID NO: 6137, SEQ ID NO: 6141, SEQ ID NO: 6144, SEQ ID NO: 6145, SEQ ID NO: 6147, SEQ ID NO: 6154, SEQ ID NO: 6167, SEQ ID NO: 6168, SEQ ID NO: 6170, SEQ ID NO: 6173, SEQ ID NO: 6178, and SEQ ID NO: 6181.

# Appendix B

**Claims as originally filed in the Preliminary Amendment of October 10, 2000**

8. A microarray having a substrate with a surface comprising $10^3$ nucleic acid molecules or more where at least 10% of the nucleic acid molecules are different and at least about 250 nucleotide residues and complementary to a molecule having a sequence selected from the group consisting of SEQ ID NO: 5776 and SEQ ID NO: 5781 and SEQ ID NO: 5782 and SEQ ID NO: 5783 and SEQ ID NO: 5786 and SEQ ID NO: 5787 and SEQ ID NO: 5800 and SEQ ID NO: 5815 and SEQ ID NO: 5818 and SEQ ID NO: 5821 and SEQ ID NO: 5823 and SEQ ID NO: 5828 and SEQ ID NO: 5830 and SEQ ID NO: 5836 and SEQ ID NO: 5838 and SEQ ID NO: 5840 and SEQ ID NO: 5845 and SEQ ID NO: 5849 and SEQ ID NO: 5850 and SEQ ID NO: 5851 and SEQ ID NO: 5859 and SEQ ID NO: 5863 and SEQ ID NO: 5868 and SEQ ID NO: 5874 and SEQ ID NO: 5875 and SEQ ID NO: 5877 and SEQ ID NO: 5893 and SEQ ID NO: 5896 and SEQ ID NO: 5901 and SEQ ID NO: 5909 and SEQ ID NO: 5922 and SEQ ID NO: 5926 and SEQ ID NO: 5928 and SEQ ID NO: 5931 and SEQ ID NO: 5936 and SEQ ID NO: 5937 and SEQ ID NO: 5939 and SEQ ID NO: 5941 and SEQ ID NO: 5950 and SEQ ID NO: 5955 and SEQ ID NO: 5956 and SEQ ID NO: 5963 and SEQ ID NO: 5973 and SEQ ID NO: 5974 and SEQ ID NO: 5991 and SEQ ID NO: 5994 and SEQ ID NO: 5999 and SEQ ID NO: 6000 and SEQ ID NO: 6001 and SEQ ID NO: 6005 and SEQ ID NO: 6006 and SEQ ID NO: 6007 and SEQ ID NO: 6011 and SEQ ID NO: 6017 and SEQ ID NO: 6022 and SEQ ID NO: 6023 and SEQ ID NO: 6030 and SEQ ID NO: 6033 and SEQ ID NO: 6059 and SEQ ID NO: 6065 and SEQ ID NO: 6089 and SEQ ID NO: 6091 and SEQ ID NO: 6106 and SEQ ID NO: 6107 and SEQ ID NO: 6110 and SEQ ID NO: 6117 and SEQ ID NO: 6121 and SEQ ID NO: 6124 and SEQ ID NO: 6137 and SEQ ID NO: 6154 and SEQ ID NO: 6167 and SEQ ID NO: 6168 and SEQ ID NO: 6170 and SEQ ID NO: 6173 and SEQ ID NO: 6178 and SEQ ID NO: 6181 and SEQ ID NO: 6188 and SEQ ID NO: 6195 and SEQ ID NO: 6196 and SEQ ID NO: 6205 and SEQ ID NO: 6211 and SEQ ID NO: 6212 and SEQ ID NO: 6214 and SEQ ID NO: 6234 and SEQ ID NO: 6241 and SEQ ID NO: 6245 and SEQ ID NO: 6251 and SEQ ID NO: 6256 and SEQ ID NO: 6261 and SEQ ID NO: 6270 and SEQ ID NO: 6272 and SEQ ID NO: 6278 and SEQ ID NO: 6283 and SEQ ID NO: 6286 and SEQ ID NO: 6288 and SEQ ID NO: 6289 and SEQ ID NO: 6291 and SEQ ID NO: 6292 and SEQ ID NO: 6293 and SEQ ID NO:

6295 and SEQ ID NO: 6302 and SEQ ID NO: 6309 and SEQ ID NO: 6316 and SEQ ID NO: 6321 and SEQ ID NO: 6324 and SEQ ID NO: 6332 and SEQ ID NO: 6337 and SEQ ID NO: 6347 and SEQ ID NO: 6348 and SEQ ID NO: 6352 and SEQ ID NO: 6355 and SEQ ID NO: 6358 and SEQ ID NO: 6361 and SEQ ID NO: 6363 and SEQ ID NO: 6367 and SEQ ID NO: 6369 and SEQ ID NO: 6371 and SEQ ID NO: 6375 and SEQ ID NO: 6377 and SEQ ID NO: 6385 and SEQ ID NO: 6405 and SEQ ID NO: 6416 and SEQ ID NO: 6418 and SEQ ID NO: 6425 and SEQ ID NO: 6433 and SEQ ID NO: 6445 and SEQ ID NO: 6451 and SEQ ID NO: 6454 and SEQ ID NO: 6459 and SEQ ID NO: 6462 and SEQ ID NO: 6464 and SEQ ID NO: 6465 and SEQ ID NO: 6466 and SEQ ID NO: 6476 and SEQ ID NO: 6479 and SEQ ID NO: 6481 and SEQ ID NO: 6482 and SEQ ID NO: 6483 and SEQ ID NO: 6489 and SEQ ID NO: 6497 and SEQ ID NO: 6502 and SEQ ID NO: 6514 and SEQ ID NO: 6521 and SEQ ID NO: 6529 and SEQ ID NO: 6530 and SEQ ID NO: 6535 and SEQ ID NO: 6540 and SEQ ID NO: 6553 and SEQ ID NO: 6556 and SEQ ID NO: 6564 and SEQ ID NO: 6565 and SEQ ID NO: 6571 and SEQ ID NO: 6598 and SEQ ID NO: 6603 and SEQ ID NO: 6604 and SEQ ID NO: 6606 and SEQ ID NO: 6611 and SEQ ID NO: 6613 and SEQ ID NO: 6620 and SEQ ID NO: 6628 and SEQ ID NO: 6633 and SEQ ID NO: 6639 and SEQ ID NO: 6640 and SEQ ID NO: 6643 and SEQ ID NO: 6651 and SEQ ID NO: 6652 and SEQ ID NO: 6654 and SEQ ID NO: 6657 and SEQ ID NO: 6659 and SEQ ID NO: 6661 and SEQ ID NO: 6664 and SEQ ID NO: 6668 and SEQ ID NO: 6670 and SEQ ID NO: 6671 and SEQ ID NO: 6674 and SEQ ID NO: 6680 and SEQ ID NO: 6685 and SEQ ID NO: 6686 and SEQ ID NO: 6688 and SEQ ID NO: 6691 and SEQ ID NO: 6692 and SEQ ID NO: 6696 and SEQ ID NO: 6697 and SEQ ID NO: 6702 and SEQ ID NO: 6704 and SEQ ID NO: 6711 and SEQ ID NO: 6716 and SEQ ID NO: 6724 and SEQ ID NO: 6726 and SEQ ID NO: 6728 and SEQ ID NO: 6739 and SEQ ID NO: 6742 and SEQ ID NO: 6744 and SEQ ID NO: 6747 and SEQ ID NO: 6764 and SEQ ID NO: 6766 and SEQ ID NO: 6770 and SEQ ID NO: 6772 and SEQ ID NO: 6773 and SEQ ID NO: 6778 and SEQ ID NO: 6781 and SEQ ID NO: 6782 and SEQ ID NO: 6790 and SEQ ID NO: 6792 and SEQ ID NO: 6841 and SEQ ID NO: 6870 and SEQ ID NO: 6871 and SEQ ID NO: 6886 and SEQ ID NO: 6894 and SEQ ID NO: 6904 and SEQ ID NO: 6906 and SEQ ID NO: 6923 and SEQ ID NO: 6931 and SEQ ID NO: 6934 and SEQ ID NO: 6938 and SEQ ID NO: 6939 and SEQ ID NO: 6949 and SEQ ID NO: 6953 and SEQ ID NO: 6961 and SEQ ID NO: 6965 and SEQ ID NO: 6978 and SEQ ID NO: 6991 and SEQ ID NO: 7000 and SEQ ID NO:

7002 and SEQ ID NO: 7036 and SEQ ID NO: 7050 and SEQ ID NO: 7053 and SEQ ID NO: 7062 and SEQ ID NO: 7070 and SEQ ID NO: 7078 and SEQ ID NO: 7083 and SEQ ID NO: 7096 and SEQ ID NO: 7100 and SEQ ID NO: 7106 and SEQ ID NO: 7107 and SEQ ID NO: 7134 and SEQ ID NO: 7144 and SEQ ID NO: 7161 and SEQ ID NO: 7164 and SEQ ID NO: 7178 and SEQ ID NO: 7206 and SEQ ID NO: 7220 and SEQ ID NO: 7221 and SEQ ID NO: 7224 and SEQ ID NO: 7228 and SEQ ID NO: 7229 and SEQ ID NO: 7241 and SEQ ID NO: 7246 and SEQ ID NO: 7248 and SEQ ID NO: 7249 and SEQ ID NO: 7254 and SEQ ID NO: 7261 and SEQ ID NO: 7267 and SEQ ID NO: 7277 and SEQ ID NO: 7332 and SEQ ID NO: 7338 and SEQ ID NO: 7351 and SEQ ID NO: 7357 and SEQ ID NO: 7369 and SEQ ID NO: 7378 and SEQ ID NO: 7380 and SEQ ID NO: 7384 and SEQ ID NO: 7386 and SEQ ID NO: 7395 and SEQ ID NO: 7438 and SEQ ID NO: 7444 and SEQ ID NO: 7447 and SEQ ID NO: 7461 and SEQ ID NO: 7463 and SEQ ID NO: 7465 and SEQ ID NO: 7468 and SEQ ID NO: 7478 and SEQ ID NO: 7490 and SEQ ID NO: 7491 and SEQ ID NO: 7492 and SEQ ID NO: 7509 and SEQ ID NO: 7514 and SEQ ID NO: 7536 and SEQ ID NO: 7559 and SEQ ID NO: 7563 and SEQ ID NO: 7565 and SEQ ID NO: 7572 and SEQ ID NO: 7576 and SEQ ID NO: 7590 and SEQ ID NO: 7592 and SEQ ID NO: 7594 and SEQ ID NO: 7596 and SEQ ID NO: 7602 and SEQ ID NO: 7612 and SEQ ID NO: 7617 and SEQ ID NO: 7618 and SEQ ID NO: 7622 and SEQ ID NO: 7624 and SEQ ID NO: 7627 and SEQ ID NO: 7631 and SEQ ID NO: 7632 and SEQ ID NO: 7644 and SEQ ID NO: 7646 and SEQ ID NO: 7655 and SEQ ID NO: 7657 and SEQ ID NO: 7659 and SEQ ID NO: 7677 and SEQ ID NO: 7682 and SEQ ID NO: 7685 and SEQ ID NO: 7690 and SEQ ID NO: 7694 and SEQ ID NO: 7697 and SEQ ID NO: 7701 and SEQ ID NO: 7702 and SEQ ID NO: 7703 and SEQ ID NO: 7707 and SEQ ID NO: 7708 and SEQ ID NO: 7711 and SEQ ID NO: 7715 and SEQ ID NO: 7718 and SEQ ID NO: 7721 and SEQ ID NO: 7723 and SEQ ID NO: 7724 and SEQ ID NO: 7729 and SEQ ID NO: 7736 and SEQ ID NO: 7745 and SEQ ID NO: 7749 and SEQ ID NO: 7757 and SEQ ID NO: 7761 and SEQ ID NO: 7770 and SEQ ID NO: 7772 and SEQ ID NO: 7777 and SEQ ID NO: 7782 and SEQ ID NO: 7791 and SEQ ID NO: 7795 and SEQ ID NO: 7796 and SEQ ID NO: 7800 and SEQ ID NO: 7801 and SEQ ID NO: 7802 and SEQ ID NO: 7808 and SEQ ID NO: 7809 and SEQ ID NO: 7813 and SEQ ID NO: 7818 and SEQ ID NO: 7823 and SEQ ID NO: 7825 and SEQ ID NO: 7826 and SEQ ID NO: 7827 and SEQ ID NO: 7831 and SEQ ID NO: 7837 and SEQ ID NO: 7844 and SEQ ID NO: 7845 and SEQ ID NO: 7847 and SEQ ID NO:

7849 and SEQ ID NO: 7852 and SEQ ID NO: 7856 and SEQ ID NO: 7860 and SEQ ID NO: 7862 and SEQ ID NO: 7863 and SEQ ID NO: 7865 and SEQ ID NO: 7867 and SEQ ID NO: 7870 and SEQ ID NO: 7872 and SEQ ID NO: 7880 and SEQ ID NO: 7883 and SEQ ID NO: 7884 and SEQ ID NO: 7885 and SEQ ID NO: 7886 and SEQ ID NO: 7888 and SEQ ID NO: 7889 and SEQ ID NO: 7894 and SEQ ID NO: 7895 and SEQ ID NO: 7896 and SEQ ID NO: 7901 and SEQ ID NO: 7905 and SEQ ID NO: 7908 and SEQ ID NO: 7918 and SEQ ID NO: 7928 and SEQ ID NO: 7931 and SEQ ID NO: 7937 and SEQ ID NO: 7947 and SEQ ID NO: 7952 and SEQ ID NO: 7959 and SEQ ID NO: 7962 and SEQ ID NO: 7975 and SEQ ID NO: 7987 and SEQ ID NO: 7989 and SEQ ID NO: 7992 and SEQ ID NO: 7997 and SEQ ID NO: 7998 and SEQ ID NO: 8002 and SEQ ID NO: 8006 and SEQ ID NO: 8007 and SEQ ID NO: 8008 and SEQ ID NO: 8010 and SEQ ID NO: 8015 and SEQ ID NO: 8017 and SEQ ID NO: 8018 and SEQ ID NO: 8020 and SEQ ID NO: 8022 and SEQ ID NO: 8024 and SEQ ID NO: 8026 and SEQ ID NO: 8043 and SEQ ID NO: 8048 and SEQ ID NO: 8053 and SEQ ID NO: 8063 and SEQ ID NO: 8064 and SEQ ID NO: 8066 and SEQ ID NO: 8095 and SEQ ID NO: 8098 and SEQ ID NO: 8099 and SEQ ID NO: 8103 and SEQ ID NO: 8126 and SEQ ID NO: 8145 and SEQ ID NO: 8153 and SEQ ID NO: 8155 and SEQ ID NO: 8157 and SEQ ID NO: 8161 and SEQ ID NO: 8171 and SEQ ID NO: 8175 and SEQ ID NO: 8180 and SEQ ID NO: 8184 and SEQ ID NO: 8192 and SEQ ID NO: 8198 and SEQ ID NO: 8199 and SEQ ID NO: 8201 and SEQ ID NO: 8212 and SEQ ID NO: 8216 and SEQ ID NO: 8222 and SEQ ID NO: 8224 and SEQ ID NO: 8225 and SEQ ID NO: 8228 and SEQ ID NO: 8238 and SEQ ID NO: 8242 and SEQ ID NO: 8256 and SEQ ID NO: 8259 and SEQ ID NO: 8274 and SEQ ID NO: 8277 and SEQ ID NO: 8278 and SEQ ID NO: 8289 and SEQ ID NO: 8292 and SEQ ID NO: 8297 and SEQ ID NO: 8301 and SEQ ID NO: 8317 and SEQ ID NO: 8329 and SEQ ID NO: 8333 and SEQ ID NO: 8334 and SEQ ID NO: 8335 and SEQ ID NO: 8351 and SEQ ID NO: 8355 and SEQ ID NO: 8374 and SEQ ID NO: 8377 and SEQ ID NO: 8379 and SEQ ID NO: 8383 and SEQ ID NO: 8394 and SEQ ID NO: 8406 and SEQ ID NO: 8447 and SEQ ID NO: 8452 and SEQ ID NO: 8455 and SEQ ID NO: 8458 and SEQ ID NO: 8465 and SEQ ID NO: 8468 and SEQ ID NO: 8472 and SEQ ID NO: 8479 and SEQ ID NO: 8482 and SEQ ID NO: 8487 and SEQ ID NO: 8492 and SEQ ID NO: 8500 and SEQ ID NO: 8503 and SEQ ID NO: 8507 and SEQ ID NO: 8511 and SEQ ID NO: 8512 and SEQ ID NO: 8517 and SEQ ID NO: 8518 and SEQ ID NO: 8529 and SEQ ID NO: 8530 and SEQ ID NO: 8538 and SEQ ID NO:

8542 and SEQ ID NO: 8553 and SEQ ID NO: 8554 and SEQ ID NO: 8556 and SEQ ID NO: 8560 and SEQ ID NO: 8568 and SEQ ID NO: 8569 and SEQ ID NO: 8578 and SEQ ID NO: 8579 and SEQ ID NO: 8580 and SEQ ID NO: 8583 and SEQ ID NO: 8584 and SEQ ID NO: 8585 and SEQ ID NO: 8587 and SEQ ID NO: 8590 and SEQ ID NO: 8601 and SEQ ID NO: 8607 and SEQ ID NO: 8611 and SEQ ID NO: 8616 and SEQ ID NO: 8624 and SEQ ID NO: 8625 and SEQ ID NO: 8631 and SEQ ID NO: 8632 and SEQ ID NO: 8639 and SEQ ID NO: 8644 and SEQ ID NO: 8665.

9. A microarray according to claim 8 where at least 75% of the nucleic acid molecules are different and at least about 250 nucleotide residues and complementary to a molecule having a sequence selected from said group.

10. A microarray according to claim 8 where at least 95% of the nucleic acid molecules are different and at least about 250 nucleotide residues and complementary to a molecule having a sequence selected from said group.

11. A microarray comprising nucleic acid molecules that are different and at least about 250 nucleotide residues, wherein said nucleic acid molecules comprise nucleic acid sequences complementary to SEQ ID NO: 5776 and SEQ ID NO: 5781 and SEQ ID NO: 5782 and SEQ ID NO: 5783 and SEQ ID NO: 5786 and SEQ ID NO: 5787 and SEQ ID NO: 5800 and SEQ ID NO: 5815 and SEQ ID NO: 5818 and SEQ ID NO: 5821 and SEQ ID NO: 5823 and SEQ ID NO: 5828 and SEQ ID NO: 5830 and SEQ ID NO: 5836 and SEQ ID NO: 5838 and SEQ ID NO: 5840 and SEQ ID NO: 5845 and SEQ ID NO: 5849 and SEQ ID NO: 5850 and SEQ ID NO: 5851 and SEQ ID NO: 5859 and SEQ ID NO: 5863 and SEQ ID NO: 5868 and SEQ ID NO: 5874 and SEQ ID NO: 5875 and SEQ ID NO: 5877 and SEQ ID NO: 5893 and SEQ ID NO: 5896 and SEQ ID NO: 5901 and SEQ ID NO: 5909 and SEQ ID NO: 5922 and SEQ ID NO: 5926 and SEQ ID NO: 5928 and SEQ ID NO: 5931 and SEQ ID NO: 5936 and SEQ ID NO: 5937 and SEQ ID NO: 5939 and SEQ ID NO: 5941 and SEQ ID NO: 5950 and SEQ ID NO: 5955 and SEQ ID NO: 5956 and SEQ ID NO: 5963 and SEQ ID NO: 5973 and SEQ ID NO: 5974 and SEQ ID NO: 5991 and SEQ ID NO: 5994 and SEQ ID NO: 5999 and SEQ ID NO: 6000 and SEQ ID NO: 6001 and SEQ ID NO: 6005 and SEQ ID NO: 6006 and SEQ ID NO: 6007 and SEQ ID NO: 6011 and SEQ ID NO: 6017 and SEQ ID NO: 6022 and SEQ ID

NO: 6023 and SEQ ID NO: 6030 and SEQ ID NO: 6033 and SEQ ID NO: 6059 and SEQ ID NO: 6065 and SEQ ID NO: 6089 and SEQ ID NO: 6091 and SEQ ID NO: 6106 and SEQ ID NO: 6107 and SEQ ID NO: 6110 and SEQ ID NO: 6117 and SEQ ID NO: 6121 and SEQ ID NO: 6124 and SEQ ID NO: 6137 and SEQ ID NO: 6154 and SEQ ID NO: 6167 and SEQ ID NO: 6168 and SEQ ID NO: 6170 and SEQ ID NO: 6173 and SEQ ID NO: 6178 and SEQ ID NO: 6181 and SEQ ID NO: 6188 and SEQ ID NO: 6195 and SEQ ID NO: 6196 and SEQ ID NO: 6205 and SEQ ID NO: 6211 and SEQ ID NO: 6212 and SEQ ID NO: 6214 and SEQ ID NO: 6234 and SEQ ID NO: 6241 and SEQ ID NO: 6245 and SEQ ID NO: 6251 and SEQ ID NO: 6256 and SEQ ID NO: 6261 and SEQ ID NO: 6270 and SEQ ID NO: 6272 and SEQ ID NO: 6278 and SEQ ID NO: 6283 and SEQ ID NO: 6286 and SEQ ID NO: 6288 and SEQ ID NO: 6289 and SEQ ID NO: 6291 and SEQ ID NO: 6292 and SEQ ID NO: 6293 and SEQ ID NO: 6295 and SEQ ID NO: 6302 and SEQ ID NO: 6309 and SEQ ID NO: 6316 and SEQ ID NO: 6321 and SEQ ID NO: 6324 and SEQ ID NO: 6332 and SEQ ID NO: 6337 and SEQ ID NO: 6347 and SEQ ID NO: 6348 and SEQ ID NO: 6352 and SEQ ID NO: 6355 and SEQ ID NO: 6358 and SEQ ID NO: 6361 and SEQ ID NO: 6363 and SEQ ID NO: 6367 and SEQ ID NO: 6369 and SEQ ID NO: 6371 and SEQ ID NO: 6375 and SEQ ID NO: 6377 and SEQ ID NO: 6385 and SEQ ID NO: 6405 and SEQ ID NO: 6416 and SEQ ID NO: 6418 and SEQ ID NO: 6425 and SEQ ID NO: 6433 and SEQ ID NO: 6445 and SEQ ID NO: 6451 and SEQ ID NO: 6454 and SEQ ID NO: 6459 and SEQ ID NO: 6462 and SEQ ID NO: 6464 and SEQ ID NO: 6465 and SEQ ID NO: 6466 and SEQ ID NO: 6476 and SEQ ID NO: 6479 and SEQ ID NO: 6481 and SEQ ID NO: 6482 and SEQ ID NO: 6483 and SEQ ID NO: 6489 and SEQ ID NO: 6497 and SEQ ID NO: 6502 and SEQ ID NO: 6514 and SEQ ID NO: 6521 and SEQ ID NO: 6529 and SEQ ID NO: 6530 and SEQ ID NO: 6535 and SEQ ID NO: 6540 and SEQ ID NO: 6553 and SEQ ID NO: 6556 and SEQ ID NO: 6564 and SEQ ID NO: 6565 and SEQ ID NO: 6571 and SEQ ID NO: 6598 and SEQ ID NO: 6603 and SEQ ID NO: 6604 and SEQ ID NO: 6606 and SEQ ID NO: 6611 and SEQ ID NO: 6613 and SEQ ID NO: 6620 and SEQ ID NO: 6628 and SEQ ID NO: 6633 and SEQ ID NO: 6639 and SEQ ID NO: 6640 and SEQ ID NO: 6643 and SEQ ID NO: 6651 and SEQ ID NO: 6652 and SEQ ID NO: 6654 and SEQ ID NO: 6657 and SEQ ID NO: 6659 and SEQ ID NO: 6661 and SEQ ID NO: 6664 and SEQ ID NO: 6668 and SEQ ID NO: 6670 and SEQ ID NO: 6671 and SEQ ID NO: 6674 and SEQ ID NO: 6680 and SEQ ID NO: 6685 and SEQ ID NO: 6686 and SEQ ID NO: 6688 and SEQ ID

NO: 6691 and SEQ ID NO: 6692 and SEQ ID NO: 6696 and SEQ ID NO: 6697 and SEQ ID NO: 6702 and SEQ ID NO: 6704 and SEQ ID NO: 6711 and SEQ ID NO: 6716 and SEQ ID NO: 6724 and SEQ ID NO: 6726 and SEQ ID NO: 6728 and SEQ ID NO: 6739 and SEQ ID NO: 6742 and SEQ ID NO: 6744 and SEQ ID NO: 6747 and SEQ ID NO: 6764 and SEQ ID NO: 6766 and SEQ ID NO: 6770 and SEQ ID NO: 6772 and SEQ ID NO: 6773 and SEQ ID NO: 6778 and SEQ ID NO: 6781 and SEQ ID NO: 6782 and SEQ ID NO: 6790 and SEQ ID NO: 6792 and SEQ ID NO: 6841 and SEQ ID NO: 6870 and SEQ ID NO: 6871 and SEQ ID NO: 6886 and SEQ ID NO: 6894 and SEQ ID NO: 6904 and SEQ ID NO: 6906 and SEQ ID NO: 6923 and SEQ ID NO: 6931 and SEQ ID NO: 6934 and SEQ ID NO: 6938 and SEQ ID NO: 6939 and SEQ ID NO: 6949 and SEQ ID NO: 6953 and SEQ ID NO: 6961 and SEQ ID NO: 6965 and SEQ ID NO: 6978 and SEQ ID NO: 6991 and SEQ ID NO: 7000 and SEQ ID NO: 7002 and SEQ ID NO: 7036 and SEQ ID NO: 7050 and SEQ ID NO: 7053 and SEQ ID NO: 7062 and SEQ ID NO: 7070 and SEQ ID NO: 7078 and SEQ ID NO: 7083 and SEQ ID NO: 7096 and SEQ ID NO: 7100 and SEQ ID NO: 7106 and SEQ ID NO: 7107 and SEQ ID NO: 7134 and SEQ ID NO: 7144 and SEQ ID NO: 7161 and SEQ ID NO: 7164 and SEQ ID NO: 7178 and SEQ ID NO: 7206 and SEQ ID NO: 7220 and SEQ ID NO: 7221 and SEQ ID NO: 7224 and SEQ ID NO: 7228 and SEQ ID NO: 7229 and SEQ ID NO: 7241 and SEQ ID NO: 7246 and SEQ ID NO: 7248 and SEQ ID NO: 7249 and SEQ ID NO: 7254 and SEQ ID NO: 7261 and SEQ ID NO: 7267 and SEQ ID NO: 7277 and SEQ ID NO: 7332 and SEQ ID NO: 7338 and SEQ ID NO: 7351 and SEQ ID NO: 7357 and SEQ ID NO: 7369 and SEQ ID NO: 7378 and SEQ ID NO: 7380 and SEQ ID NO: 7384 and SEQ ID NO: 7386 and SEQ ID NO: 7395 and SEQ ID NO: 7438 and SEQ ID NO: 7444 and SEQ ID NO: 7447 and SEQ ID NO: 7461 and SEQ ID NO: 7463 and SEQ ID NO: 7465 and SEQ ID NO: 7468 and SEQ ID NO: 7478 and SEQ ID NO: 7490 and SEQ ID NO: 7491 and SEQ ID NO: 7492 and SEQ ID NO: 7509 and SEQ ID NO: 7514 and SEQ ID NO: 7536 and SEQ ID NO: 7559 and SEQ ID NO: 7563 and SEQ ID NO: 7565 and SEQ ID NO: 7572 and SEQ ID NO: 7576 and SEQ ID NO: 7590 and SEQ ID NO: 7592 and SEQ ID NO: 7594 and SEQ ID NO: 7596 and SEQ ID NO: 7602 and SEQ ID NO: 7612 and SEQ ID NO: 7617 and SEQ ID NO: 7618 and SEQ ID NO: 7622 and SEQ ID NO: 7624 and SEQ ID NO: 7627 and SEQ ID NO: 7631 and SEQ ID NO: 7632 and SEQ ID NO: 7644 and SEQ ID NO: 7646 and SEQ ID NO: 7655 and SEQ ID NO: 7657 and SEQ ID NO: 7659 and SEQ ID NO: 7677 and SEQ ID NO: 7682 and SEQ ID

NO: 7685 and SEQ ID NO: 7690 and SEQ ID NO: 7694 and SEQ ID NO: 7697 and SEQ ID NO: 7701 and SEQ ID NO: 7702 and SEQ ID NO: 7703 and SEQ ID NO: 7707 and SEQ ID NO: 7708 and SEQ ID NO: 7711 and SEQ ID NO: 7715 and SEQ ID NO: 7718 and SEQ ID NO: 7721 and SEQ ID NO: 7723 and SEQ ID NO: 7724 and SEQ ID NO: 7729 and SEQ ID NO: 7736 and SEQ ID NO: 7745 and SEQ ID NO: 7749 and SEQ ID NO: 7757 and SEQ ID NO: 7761 and SEQ ID NO: 7770 and SEQ ID NO: 7772 and SEQ ID NO: 7777 and SEQ ID NO: 7782 and SEQ ID NO: 7791 and SEQ ID NO: 7795 and SEQ ID NO: 7796 and SEQ ID NO: 7800 and SEQ ID NO: 7801 and SEQ ID NO: 7802 and SEQ ID NO: 7808 and SEQ ID NO: 7809 and SEQ ID NO: 7813 and SEQ ID NO: 7818 and SEQ ID NO: 7823 and SEQ ID NO: 7825 and SEQ ID NO: 7826 and SEQ ID NO: 7827 and SEQ ID NO: 7831 and SEQ ID NO: 7837 and SEQ ID NO: 7844 and SEQ ID NO: 7845 and SEQ ID NO: 7847 and SEQ ID NO: 7849 and SEQ ID NO: 7852 and SEQ ID NO: 7856 and SEQ ID NO: 7860 and SEQ ID NO: 7862 and SEQ ID NO: 7863 and SEQ ID NO: 7865 and SEQ ID NO: 7867 and SEQ ID NO: 7870 and SEQ ID NO: 7872 and SEQ ID NO: 7880 and SEQ ID NO: 7883 and SEQ ID NO: 7884 and SEQ ID NO: 7885 and SEQ ID NO: 7886 and SEQ ID NO: 7888 and SEQ ID NO: 7889 and SEQ ID NO: 7894 and SEQ ID NO: 7895 and SEQ ID NO: 7896 and SEQ ID NO: 7901 and SEQ ID NO: 7905 and SEQ ID NO: 7908 and SEQ ID NO: 7918 and SEQ ID NO: 7928 and SEQ ID NO: 7931 and SEQ ID NO: 7937 and SEQ ID NO: 7947 and SEQ ID NO: 7952 and SEQ ID NO: 7959 and SEQ ID NO: 7962 and SEQ ID NO: 7975 and SEQ ID NO: 7987 and SEQ ID NO: 7989 and SEQ ID NO: 7992 and SEQ ID NO: 7997 and SEQ ID NO: 7998 and SEQ ID NO: 8002 and SEQ ID NO: 8006 and SEQ ID NO: 8007 and SEQ ID NO: 8008 and SEQ ID NO: 8010 and SEQ ID NO: 8015 and SEQ ID NO: 8017 and SEQ ID NO: 8018 and SEQ ID NO: 8020 and SEQ ID NO: 8022 and SEQ ID NO: 8024 and SEQ ID NO: 8026 and SEQ ID NO: 8043 and SEQ ID NO: 8048 and SEQ ID NO: 8053 and SEQ ID NO: 8063 and SEQ ID NO: 8064 and SEQ ID NO: 8066 and SEQ ID NO: 8095 and SEQ ID NO: 8098 and SEQ ID NO: 8099 and SEQ ID NO: 8103 and SEQ ID NO: 8126 and SEQ ID NO: 8145 and SEQ ID NO: 8153 and SEQ ID NO: 8155 and SEQ ID NO: 8157 and SEQ ID NO: 8161 and SEQ ID NO: 8171 and SEQ ID NO: 8175 and SEQ ID NO: 8180 and SEQ ID NO: 8184 and SEQ ID NO: 8192 and SEQ ID NO: 8198 and SEQ ID NO: 8199 and SEQ ID NO: 8201 and SEQ ID NO: 8212 and SEQ ID NO: 8216 and SEQ ID NO: 8222 and SEQ ID NO: 8224 and SEQ ID NO: 8225 and SEQ ID NO: 8228 and SEQ ID NO: 8238 and SEQ ID

NO: 8242 and SEQ ID NO: 8256 and SEQ ID NO: 8259 and SEQ ID NO: 8274 and SEQ ID NO: 8277 and SEQ ID NO: 8278 and SEQ ID NO: 8289 and SEQ ID NO: 8292 and SEQ ID NO: 8297 and SEQ ID NO: 8301 and SEQ ID NO: 8317 and SEQ ID NO: 8329 and SEQ ID NO: 8333 and SEQ ID NO: 8334 and SEQ ID NO: 8335 and SEQ ID NO: 8351 and SEQ ID NO: 8355 and SEQ ID NO: 8374 and SEQ ID NO: 8377 and SEQ ID NO: 8379 and SEQ ID NO: 8383 and SEQ ID NO: 8394 and SEQ ID NO: 8406 and SEQ ID NO: 8447 and SEQ ID NO: 8452 and SEQ ID NO: 8455 and SEQ ID NO: 8458 and SEQ ID NO: 8465 and SEQ ID NO: 8468 and SEQ ID NO: 8472 and SEQ ID NO: 8479 and SEQ ID NO: 8482 and SEQ ID NO: 8487 and SEQ ID NO: 8492 and SEQ ID NO: 8500 and SEQ ID NO: 8503 and SEQ ID NO: 8507 and SEQ ID NO: 8511 and SEQ ID NO: 8512 and SEQ ID NO: 8517 and SEQ ID NO: 8518 and SEQ ID NO: 8529 and SEQ ID NO: 8530 and SEQ ID NO: 8538 and SEQ ID NO: 8542 and SEQ ID NO: 8553 and SEQ ID NO: 8554 and SEQ ID NO: 8556 and SEQ ID NO: 8560 and SEQ ID NO: 8568 and SEQ ID NO: 8569 and SEQ ID NO: 8578 and SEQ ID NO: 8579 and SEQ ID NO: 8580 and SEQ ID NO: 8583 and SEQ ID NO: 8584 and SEQ ID NO: 8585 and SEQ ID NO: 8587 and SEQ ID NO: 8590 and SEQ ID NO: 8601 and SEQ ID NO: 8607 and SEQ ID NO: 8611 and SEQ ID NO: 8616 and SEQ ID NO: 8624 and SEQ ID NO: 8625 and SEQ ID NO: 8631 and SEQ ID NO: 8632 and SEQ ID NO: 8639 and SEQ ID NO: 8644 and SEQ ID NO: 8665.